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(57) Abstract

The present invention provides a pharmaceutical product comprising an SSRI and a non–sedating anxiolytic compound which is a modulator of the benzodiazepine binding site of the human $GABA_A$ receptor, having a binding affinity (K_i) for the $\alpha 3$ subunit of the human $GABA_A$ receptor of 10 nM or less, which elicits at least a 40 % potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the $\alpha 3$ subunit of the human $GABA_A$ receptor, and which elicits at most a 30 % potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the $\alpha 1$ submit of the human $GABA_A$ receptor for simultaneous, separate or sequential administration.

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COMBINATION OF A GABA-A ALPHA 2/3 AGONIST AND A SELECTIVE SEROTONIN REUPTAKE INHIBITOR

The present invention relates to a pharmaceutical product comprising a $GABA_A$ α2/3 agonist and an SSRI.

Selective serotonin reuptake inhibitors (SSRIs) are a new class of antidepressant drugs.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) $GABA_A$ receptors, which are members of the ligand-gated ion channel superfamily; and (2) $GABA_B$ receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual $GABA_A$ receptor subunits were cloned the number of known members of the mammalian family has grown to thirteen (six α subunits, three β subunits, three γ subunits and one δ subunit). It may be that further subunits remain to be discovered; however, none has been reported since 1993.

Although knowledge of the diversity of the $GABA_A$ receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, a β subunit and a γ subunit constitute the minimum requirement for forming a fully functional $GABA_A$ receptor expressed by transiently transfecting cDNAs into cells. As indicated above, a δ subunit also exists, but is present only to a minor extent in $GABA_A$ receptor populations.

Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native $GABA_A$ receptor exists in pentameric form. The selection of at least one α, one β and one γ subunit from a repertoire of thirteen allows for the possible existence of more than 10,000 pentameric subunit combinations. Moreover, this calculation overlooks the additional permutations that would be possible if the arrangement of subunits

around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include, amongst many others, $\alpha1\beta2\gamma2$, $\alpha2\beta2/3\gamma2$, $\alpha3\beta\gamma2/3$, $\alpha2\beta\gamma1$, $\alpha5\beta3\gamma2/3$, $\alpha6\beta\gamma2$, $\alpha6\beta\delta$ and $\alpha4\beta\delta$. Subtype assemblies containing an $\alpha1$ subunit are present in most areas of the brain and are thought to account for over 40% of $GABA_A$ receptors in the rat. Subtype assemblies containing $\alpha2$ and $\alpha3$ subunits respectively are thought to account for about 25% and 17% of $GABA_A$ receptors in the rat. Subtype assemblies containing an $\alpha5$ subunit are expressed predominantly in the hippocampus and cortex and are thought to represent about 4% of $GABA_A$ receptors in the rat.

A characteristic property of all known $GABA_A$ receptors is the presence of a number of modulatory sites, one of which is the benzodiazepine (BZ) binding site. The BZ binding site is the most explored of the $GABA_A$ receptor modulatory sites, and is the site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the $GABA_A$ receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a $GABA_A$ receptor comprising the $\alpha1$ subunit in combination with a β subunit and $\gamma2$. This is the most abundant $GABA_A$ receptor subtype, and is believed to represent almost half of all $GABA_A$ receptors in the brain.

Two other major populations are the $\alpha2\beta\gamma2$ and $\alpha3\beta\gamma2/3$ subtypes. Together these constitute approximately a further 35% of the total $GABA_A$ receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha5$-containing subtype assemblies. The physiological role of these subtypes has hitherto been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at $\alpha 1\beta\gamma 2$, $\alpha 2\beta\gamma 2$ or $\alpha 3\beta\gamma 2$ subunits will possess desirable anxiolytic properties. Compounds which are modulators of the benzodiazepine binding site of the $GABA_A$ receptor by acting as BZ agonists are referred to hereinafter as "$GABA_A$ receptor agonists". The $\alpha 1$-selective $GABA_A$ receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through $GABA_A$ receptors containing the $\alpha 1$ subunit. Accordingly, it is considered that $GABA_A$ receptor agonists which bind more effectively to the $\alpha 2$ and/or $\alpha 3$ subunit than to $\alpha 1$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Also, agents which are antagonists or inverse agonists at $\alpha 1$ might be employed to reverse sedation or hypnosis caused by $\alpha 1$ agonists.

The products of the present invention are of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; and depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder.

In DE-A-2741763, and in US Patents 4,260,755, 4,260,756 and 4,654,343, are described various classes of 1,2,4-triazolo[4,3-b]pyridazine derivatives which are alleged to be useful as anxiolytic agents. The compounds described in DE-A-2741763 and in US Patents 4,260,755 and 4,654,343 possess a phenyl substituent at the 6-position of the triazolo-pyridazine ring system. The compounds described in US Patent 4,260,756, meanwhile, possess a heteroaryl moiety at the 6- or 8-position. In none of

these publications, however, is there any disclosure or suggestion of 1,2,4-triazolo[4,3-b]pyridazine derivatives wherein the substituent at the 6-position is attached through a directly linked oxygen atom.

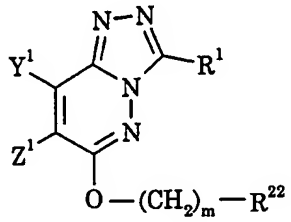
EP-A-0085840 and EP-A-0134946 describe related series of 1,2,4-triazolo[3,4-a]phthalazine derivatives which are stated to possess antianxiety activity. However, there is no disclosure nor any suggestion in either of these publications of replacing the benzo moiety of the triazolo-phthalazine ring system with any other functionality.

The present invention utilises a class of triazolo-pyridazine derivatives which possess desirable binding properties at various $GABA_A$ receptor subtypes. The GABA compounds of use in the present invention have good affinity as ligands for the α2 and/or α3 subunit of the human $GABA_A$ receptor. The GABA compounds of use in this invention may display more effective binding to the α2 and/or α3 subunit than to the α1 subunit. Desirably, the GABA compounds of use in the invention will exhibit functional selectivity in terms of a selective efficacy for the α2 and/or α3 subunit relative to the α1 subunit.

The GABA compounds of use in the present invention are $GABA_A$ receptor subtype ligands having a binding affinity (K_i) for the α2 and/or α3 subunit, as measured in the assay described hereinbelow, of 100 nM or less, typically of 50 nM or less, and ideally of 10 nM or less. The GABA compounds of use in accordance with this invention may possess at least a 2-fold, suitably at least a 5-fold, and advantageously at least a 10-fold, selective affinity for the α2 and/or α3 subunit relative to the α1 subunit. However, compounds which are unselective in terms of their binding affinity for the α2 and/or α3 subunit relative to the α1 subunit are also of use in the present invention; such compounds will desirably exhibit functional selectivity in terms of a selective efficacy for the α2 and/or α3 subunit relative to the α1 subunit.

The products of the present invention have the advantage that they surprisingly provide relief from anxiety more rapidly than would be expected from the administration of either compound alone.

The present invention thus provides a pharmaceutical product comprising an SSRI and a compound of formula I, or a salt or prodrug thereof:



(I)

wherein

Y^1 represents hydrogen or methyl;

Z^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, aryl, C_{3-7} heterocycloalkyl, heteroaryl or di(C_{1-6})alkylamino, any of which groups may be optionally substituted;

R^1 represents C_{3-7} cycloalkyl, phenyl, furyl, thienyl or pyridinyl, any of which groups may be optionally substituted;

m is 1 or 2, preferably 1; and

R^{22} represents aryl or heteroaryl, either of which groups may be optionally substituted.

The present invention also provides a compound of formula I as defined above, or a salt or prodrug thereof, wherein

Z^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl, or heteroaryl, any of which groups may be optionally substituted; and

Y^1, R^1, m and R^{22} are as defined above.

The groups Z^1, R^1 and R^{22} may be unsubstituted, or substituted by one or more, suitably by one or two, substituents. In general, the groups Z^1, R^1 and R^{22} will be unsubstituted or monosubstituted. Examples of optional substituents on the groups Z^1, R^1 and R^{22} include C_{1-6} alkyl,

aryl(C_{1-6})alkyl, pyridyl(C_{1-6})alkyl, halogen, halo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, hydroxy, hydroxymethyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl(C_{1-6})alkoxy, C_{3-7} cycloalkoxy, amino(C_{1-6})alkyl, di(C_{1-6})alkylamino(C_{1-6})alkyl, di(C_{1-6})alkylaminocarbonyl(C_{1-6})alkyl, *N*-(C_{1-6})alkylpiperidinyl, pyrrolidinyl(C_{1-6})alkyl, piperazinyl(C_{1-6})alkyl, morpholinyl(C_{1-6})alkyl, di(C_{1-6})alkylmorpholinyl(C_{1-6})alkyl and imidazolyl(C_{1-6})alkyl. Illustrative substituents include C_{1-6} alkyl, aryl(C_{1-6})alkyl, pyridyl(C_{1-6})alkyl, halogen, halo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, hydroxy, hydroxymethyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl(C_{1-6})alkoxy, di(C_{1-6})alkylamino(C_{1-6})alkyl, di(C_{1-6})alkylaminocarbonyl(C_{1-6})alkyl, morpholinyl(C_{1-6})alkyl and imidazolyl(C_{1-6})alkyl. Representative substituents include C_{1-6} alkyl, aryl(C_{1-6})alkyl, halogen, cyano, hydroxy, hydroxymethyl, C_{1-6} alkoxy and C_{3-7} cycloalkyl(C_{1-6})alkoxy for simultaneous, separate or sequential administration.

As used herein, the expression "C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, *tert*-butyl and 1,1-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy" are to be construed accordingly.

Typical C_{3-7} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The expression "C_{3-7} cycloalkyl(C_{1-6})alkyl" as used herein includes cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

Typical C_{4-7} cycloalkenyl groups include cyclobutenyl, cyclopentenyl and cyclohexenyl.

Typical aryl groups include phenyl and naphthyl, preferably phenyl.

The expression "aryl(C_{1-6})alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C_{1-6})alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, pyrazolylmethyl, oxazolylmethyl, oxazolylethyl, isoxazolylmethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl, isoquinolinylmethyl and quinoxalinylmethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine or chlorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal

salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope the use of prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Where the GABA compounds of use in the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Examples of typical optional substituents on the group R^1 include methyl, fluoro and methoxy.

Representative values of R^1 include cyclopropyl, phenyl, methylphenyl, fluorophenyl, difluorophenyl, methoxyphenyl, furyl, thienyl, methyl-thienyl and pyridinyl. Particular values include cyclopropyl, phenyl, methylphenyl, fluorophenyl, methoxyphenyl and pyridinyl. More particularly, R^1 may represent unsubstituted or monosubstituted phenyl. Most particularly, R^1 represents phenyl.

Suitably, Y^1 represents hydrogen.

Examples of typical substituents on the group Z^1 include C_{1-6} alkyl and halogen, especially methyl or chloro.

Representative values for the group Z^1 include methyl, ethyl, isopropyl, *tert*-butyl, 1,1-dimethylpropyl, methyl-cyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, cyclobutenyl, phenyl, pyrrolidinyl, methyl-pyrrolidinyl, piperidinyl,

morpholinyl, thiomorpholinyl, pyridinyl, furyl, thienyl, chloro-thienyl and diethylamino.

Particular values for the group Z^1 include methyl, ethyl, isopropyl, *tert*-butyl, methyl-cyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, phenyl, pyrrolidinyl, methyl-pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyridinyl, furyl, thienyl and chloro-thienyl.

A favoured value of Z^1 is cyclobutyl.

Examples of typical substituents on the group R^{22} include C_{1-6} alkyl, aryl(C_{1-6})alkyl, pyridyl(C_{1-6})alkyl, halogen, cyano, cyano(C_{1-6})alkyl, hydroxymethyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl(C_{1-6})alkoxy, di(C_{1-6})alkylamino(C_{1-6})alkyl, amino(C_{1-6})alkyl, di(C_{1-6})alkylaminocarbonyl(C_{1-6})alkyl, *N*-(C_{1-6})alkylpiperidinyl, pyrrolidinyl(C_{1-6})alkyl, piperazinyl(C_{1-6})alkyl and morpholinyl(C_{1-6})alkyl. Representative substituents include C_{1-6} alkyl, aryl(C_{1-6})alkyl, pyridyl(C_{1-6})alkyl, halogen, cyano, cyano(C_{1-6})alkyl, hydroxymethyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl(C_{1-6})alkoxy, di(C_{1-6})alkylamino(C_{1-6})alkyl, di(C_{1-6})alkylaminocarbonyl(C_{1-6})alkyl and morpholinyl(C_{1-6})alkyl.

Illustrative values of specific substituents on the group R^{22} include methyl, ethyl, *n*-propyl, benzyl, pyridinylmethyl, chloro, cyano, cyanomethyl, hydroxymethyl, ethoxy, cyclopropylmethoxy, dimethylaminomethyl, aminoethyl, dimethylaminoethyl, dimethylaminocarbonylmethyl, *N*-methylpiperidinyl, pyrrolidinylethyl, piperazinylethyl and morpholinylmethyl.

Representative values of specific substituents on the group R^{22} include methyl, ethyl, *n*-propyl, benzyl, pyridinylmethyl, chloro, cyano, cyanomethyl, hydroxymethyl, ethoxy, cyclopropylmethoxy, dimethylaminomethyl, dimethylaminoethyl, dimethylaminocarbonylmethyl and morpholinylmethyl.

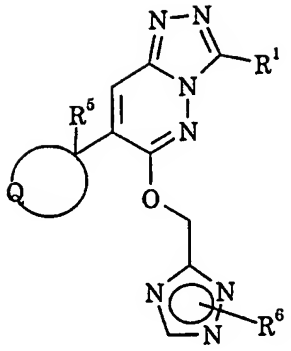
Particular values of R^{22} include cyanophenyl, hydroxymethyl-phenyl, pyrazolyl, dimethyl-pyrazolyl, methyl-isoxazolyl, thiazolyl, methyl-

thiazolyl, ethyl-thiazolyl, imidazolyl, methyl-imidazolyl, ethyl-imidazolyl, benzyl-imidazolyl, benzimidazolyl, methyl-oxadiazolyl, triazolyl, methyl-triazolyl, propyl-triazolyl, benzyl-triazolyl, pyridinylmethyl-triazolyl, cyanomethyl-triazolyl, dimethylaminomethyl-triazolyl, aminoethyl-triazolyl, dimethylaminoethyl-triazolyl, dimethylaminocarbonylmethyl-triazolyl, *N*-methylpiperidinyl-triazolyl, pyrrolidinylethyl-triazolyl, piperazinylethyl-triazolyl, morpholinylethyl-triazolyl, methyl-tetrazolyl, pyridinyl, methyl-pyridinyl, dimethyl-pyridinyl, ethoxy-pyridinyl, cyclopropylmethoxy-pyridinyl, pyridazinyl, chloro-pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl and quinoxalinyl.

Specific values of R^{22} include cyanophenyl, hydroxymethyl-phenyl, pyrazolyl, dimethyl-pyrazolyl, methyl-isoxazolyl, thiazolyl, methyl-thiazolyl, ethyl-thiazolyl, imidazolyl, methyl-imidazolyl, ethyl-imidazolyl, benzyl-imidazolyl, benzimidazolyl, methyl-oxadiazolyl, triazolyl, methyl-triazolyl, propyl-triazolyl, benzyl-triazolyl, pyridinylmethyl-triazolyl, cyanomethyl-triazolyl, dimethylaminomethyl-triazolyl, dimethylaminoethyl-triazolyl, dimethylaminocarbonylmethyl-triazolyl, morpholinylethyl-triazolyl, methyl-tetrazolyl, pyridinyl, methyl-pyridinyl, dimethyl-pyridinyl, ethoxy-pyridinyl, cyclopropylmethoxy-pyridinyl, pyridazinyl, chloro-pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl and quinoxalinyl.

A favoured value of R^{22} is methyl-triazolyl.

A particular subset of the compounds of formula I above is represented by the compounds of formula II, and pharmaceutically acceptable salts thereof:



(II)

wherein

R^1 is as defined with reference to formula I above;

Q represents the residue of a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring;

R^5 represents hydrogen or methyl; and

R^6 represents hydrogen or methyl.

In relation to formula II above, R^1 suitably represents phenyl.

In a favoured embodiment, Q suitably represents the residue of a cyclobutyl ring.

Suitably, R^5 represents hydrogen.

Suitably, R^6 represents methyl.

Specific GABA compounds of use in the present invention include:

3,7-diphenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

7,8-dimethyl-3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

7-methyl-3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

7-ethyl-3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-3,7-diphenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-7-(piperidin-1-yl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-7-(pyridin-4-yl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(pyridin-2-ylmethoxy)-7-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(pyridin-2-ylmethoxy)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-tetrazol-5-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]-pyridazine;

3,7-diphenyl-6-(2-propyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(1-propyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-imidazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methyl-3*H*-imidazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(4-methyl-4*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methyl-3*H*-1,2,3-triazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methoxyphenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methylpyridin-2-ylmethoxy)-3-phenyl-7-(piperidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(morpholin-4-yl)-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-7-(pyridin-3-yl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclohexyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclohexyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-*tert*-butyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-ethyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-*tert*-butyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-ethyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclobutyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-methyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-3-phenyl-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(pyridin-2-ylmethoxy)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2,4-difluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(pyridin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2-fluorophenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2-fluorophenyl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2,4-difluorophenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-8-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-phenyl-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methylphenyl)-7-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methylphenyl)-6-(3-methylpyridin-2-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-ethyl-1*H*-imidazol-2-ylmethoxy)-3-(4-methylphenyl)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(pyridin-2-ylmethoxy)-7-(thiomorpholin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-[2-(4-methylthiazol-5-yl)ethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

(±)-7-(2-methylpyrrolidin-1-yl)-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyridin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-isopropyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-cyclopropyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(pyridin-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(pyridin-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-(furan-3-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methyl-1,2,4-oxadiazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-phenyl-3-(thiophen-2-yl)-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(furan-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-7-(thiophen-3-yl)-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(furan-2-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(furan-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(2*H*-1,2,3-triazol-4-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyrazin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methylphenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(4-methylthiazol-2-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methylthiazol-2-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyrimidin-4-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyridazin-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(thiazol-4-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methylisoxazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(3-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyrimidin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,3-triazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclobutyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-isopropyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(4-methoxyphenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(furan-2-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(furan-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-ylacetonitrile;

7-(1-methylcyclopropyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopropyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(3-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(3-methylpyridin-2-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,3-triazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(5-methylthiophen-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

2-[3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]-*N*,*N*-dimethylacetamide;

3,7-diphenyl-6-[1-(pyridin-2-ylmethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-benzyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

2-[5-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]acetamide;

N-[2-[3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]ethyl]-*N*,*N*-dimethylamine;

3,7-diphenyl-6-(pyrimidin-5-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-[1-(2-(morpholin-4-yl)-ethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(5-chlorothiophen-2-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(5-chlorothiophen-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1*H*-benzimidazol-2-ylmethoxy)-3-(2,4-difluorophenyl)-7-(1-methylcyclopentyl)-1,2,4-triazolo[4,3-b]pyridazine;

2-[3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]ethylamine;

3,7-diphenyl-6-[1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-1,2,4-triazolo[4,3-b]pyridazine;

6-[1-(1-methylpiperidin-4-yl)-1*H*-1,2,4-triazol-3-ylmethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-[1-(2-(piperazin-1-yl)ethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2,4-difluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(cyclobut-1-enyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(furan-3-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

N,*N*-diethyl-*N*-[6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazin-7-yl]amine;

7-(1-methylcyclopentyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2,4-difluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(1,1-dimethylpropyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(4-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(4-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-7-(1-methylcyclobutyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-7-(1-methylcyclobutyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-7-(1-methylcyclobutyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-7-(1-methylcyclobutyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-8-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-8-methyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;

and salts and prodrugs thereof.

Suitable serotonin reuptake inhibitors of use in the present invention include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

The present invention also provides a pharmaceutical product comprising an SSRI and a non-sedating anxiolytic compound which is a modulator of the benzodiazepine binding site of the human $GABA_A$ receptor, having a binding affinity (K_i) for the α3 subunit of the human $GABA_A$ receptor of 10 nM or less, which elicits at least a 40% potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor, and which elicits at most a 30% potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α1 subunit of the human $GABA_A$ receptor for simultaneous, separate or sequential administration.

In this aspect of the invention, the binding affinity (K_i) of compounds for the α3 subunit of the human $GABA_A$ receptor is conveniently as measured in the assay described hereinbelow. The α3 subunit binding affinity (K_i) of compounds fulfilling this aspect of the invention is 10 nM or less, preferably 2 nM or less, and more preferably 1 nM or less.

In this aspect of the invention, the potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α3 and α1 subunits of the human $GABA_A$ receptor can conveniently be measured by procedures analogous to the protocol described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, **50**, 670-678. The procedure will suitably be carried out utilising cultures of stably transfected eukaryotic cells, typically of stably transfected mouse Ltk^- fibroblast cells.

The GABA compounds of use this aspect of the invention will elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor. Moreover, the compounds fulfilling this aspect of the invention

will elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α1 subunit of the human $GABA_A$ receptor.

The GABA compounds of use in this aspect of the invention exhibit anxiolytic activity, as demonstrated by a positive response in the elevated plus maze and conditioned suppression of drinking tests (cf. Dawson *et al.*, *Psychopharmacology*, 1995, **121**, 109-117). Moreover, the compounds fulfilling this aspect of the invention are substantially non-sedating, as confirmed by an appropriate result obtained from the response sensitivity (chain-pulling) test (cf. Bayley *et al.*, *J. Psychopharmacol.*, 1996, **10**, 206-213).

The GABA compounds of use in this aspect of the invention also exhibit anticonvulsant activity. This is demonstrated by their ability to block pentylenetetrazole-induced seizures in rats and mice, following a protocol analogous to that described by Bristow *et al.* in *J. Pharmacol. Exp. Ther.*, 1996, **279**, 492-501.

In order to elicit their behavioural effects, the compounds of use in this aspect of the invention will be brain-penetrant; in other words, these compounds will be capable of crossing the so-called "blood-brain barrier". Preferably, the compounds fulfilling this aspect of the invention will be capable of exerting their beneficial therapeutic action following administration by the oral route.

A representative GABA compound of use in this aspect of the invention is 7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine.

Suitable SSRIs are as indicated above.

Pharmaceutical compositions of use in the present invention will comprise one or both active compound(s) in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules,

sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the compositions of the present invention may be incorporated for administration orally or by injection include

aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

When administered in combination, either as a single or as separate pharmaceutical composition(s), the $GABA_A$ α2/3 agonist and the SSRI are presented in a ratio which is consistent with the manifestation of the desired effect. In particular, the ratio by weight of the $GABA_A$ α2/3 agonist and the SSRI will suitably be between 0.001 to 1 and 1000 to 1, and especially between 0.01 to 1 and 100 to 1.

A suitable dosage level for the $GABA_A$ α2/3 agonist is about 0.05 to 1500mg per day, preferably about 0.25 to 1500mg per day, and especially about 0.25 to 500mg per day. The compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day and most especially once daily.

A suitable dosage level for the SSRI is about 0.5 to 1500mg per day, preferably about 2.5 to 1000mg per day, and especially about 2.5 to 500mg per day. The compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day and most especially once daily.

It will be appreciated that the amount of the $GABA_A$ α2/3 agonist and the SSRI required for use in the treatment or prevention of depression and/or anxiety will vary not only with the particular compounds or compositions selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the patient's physician or pharmacist.

As used herein the term "patient" includes animals of economic importance such as bovine, ovine, and porcine animals, especially those that produce meat, as well as domestic animals (e.g. cats and dogs), sports animals (e.g. horses), zoo animals, and humans, the latter being preferred.

The compounds of formula I can be prepared as described in WO-A-9804559.

The GABA compounds of use with this invention potently inhibit the binding of [^{3}H]-flumazenil to the benzodiazepine binding site of human $GABA_A$ receptors containing the $\alpha 2$ or $\alpha 3$ subunit stably expressed in Ltk$^-$ cells.

Reagents

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH_2PO_4, 100 mM KCl, pH 7.4 at room temperature.
- [^{3}H]-Flumazenil (18 nM for $\alpha 1\beta 3\gamma 2$ cells; 18 nM for $\alpha 2\beta 3\gamma 2$ cells; 10 nM for $\alpha 3\beta 3\gamma 2$ cells) in assay buffer.
- Flunitrazepam 100 µM in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

Harvesting Cells

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 µl of assay buffer.

- 50 µl of [^{3}H]-flumazenil (final concentration for $\alpha1\beta3\gamma2$: 1.8 nM; for $\alpha2\beta3\gamma2$: 1.8 nM; for $\alpha3\beta3\gamma2$: 1.0 nM).
- 50 µl of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10 µM final concentration.
- 100 µl of cells.

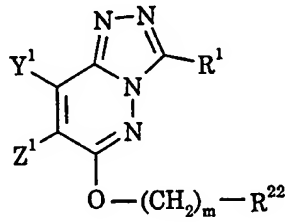
Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

The compounds of use in the present invention have a K_i value for displacement of [^{3}H]-flumazenil from the $\alpha2$ and/or $\alpha3$ subunit of the human $GABA_A$ receptor of 100 nM or less when tested in the above assay.

CLAIMS

1. A pharmaceutical product comprising an SSRI and a non-sedating anxiolytic compound which is a modulator of the benzodiazepine binding site of the human $GABA_A$ receptor, having a binding affinity (K_i) for the α3 subunit of the human $GABA_A$ receptor of 10 nM or less, which elicits at least a 40% potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor, and which elicits at most a 30% potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α1 subunit of the human $GABA_A$ receptor for simultaneous, separate or sequential administration.

2. A pharmaceutical product comprising an SSRI and a compound of formula I, or a salt or prodrug thereof:



(I)

wherein

Y^1 represents hydrogen or methyl;

Z^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, aryl, C_{3-7} heterocycloalkyl, heteroaryl or di(C_{1-6})alkylamino, any of which groups may be optionally substituted;

R^1 represents C_{3-7} cycloalkyl, phenyl, furyl, thienyl or pyridinyl, any of which groups may be optionally substituted;
m is 1 or 2, preferably 1; and

R^{22} represents aryl or heteroaryl, either of which groups may be optionally substituted.

3. A pharmaceutical product according to any one of the preceding claims wherein the SSRI is fluoxetine, paroxetine or sertraline or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 99/00161

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 98 04559 A (MERCK SHARP + DOHME LIMITED, UK;BROUGHTON, HOWARD BARFF; CARLING, WILL) 5 February 1998 see claims 1-22	1-3
A	US 4 654 343 A (J. D. ALBRIGHT ET AL) 31 March 1987 cited in the application see claims 1-15	1-3
A	US 4 260 756 A (D. B. MORAN ET AL) 7 April 1981 cited in the application see the whole document	1-3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 May 1999	19/05/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 99/00161

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 260 755 A (D. B. MORAN ET AL) 7 April 1981 cited in the application see the whole document	1-3
A	HANDLEY S: "FUTURE PROSPECTS FOR THE PHARMACOLOGICAL TREATMENT OF ANXIETY" CNS DRUGS, vol. 2, no. 5, 1 January 1994, pages 397-414, XP000650312	1-3
A	KERR ET AL: "GABA Agonists and Antagonists" MEDICINAL RESEARCH REVIEWS, vol. 12, no. 6, 6 November 1992, pages 593-636, XP002080823 see page 611 - page 613	1-3

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte 'onal Application No
PCT/GB 99/00161

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9804559 A	05-02-1998	AU 3551997 A	20-02-1998
		AU 3553997 A	20-02-1998
		WO 9804560 A	05-02-1998
US 4654343 A	31-03-1987	AU 591940 B	21-12-1989
		AU 6454986 A	07-05-1987
		DK 519486 A	01-05-1987
		EP 0223974 A	03-06-1987
		FI 864423 A	01-05-1987
		JP 62108882 A	20-05-1987
		US 4767765 A	30-08-1988
		US 4892873 A	09-01-1990
US 4260756 A	07-04-1981	EP 0029103 A	27-05-1981
		JP 56083490 A	08-07-1981
US 4260755 A	07-04-1981	NONE	